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Free radical alkylation of tri-*O*-benzoyl-6-*exo*-bromo-levoglucosan: approaches to the synthesis of okadaic acid

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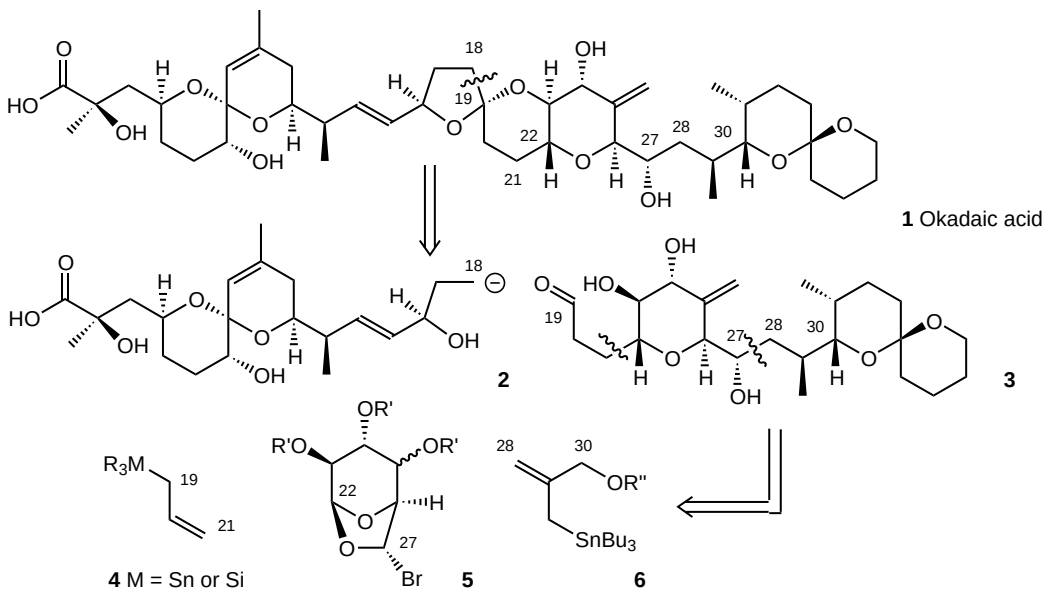
Abstract—Tri-*O*-benzoyl-6-*exo*-bromo-levoglucosan undergoes stereoselective free radical alkylation to give 6-*exo*-substituted-1,6-anhydrosugars with six contiguous chiral centres.

Total syntheses of okadaic acid **1** have been reported by Isobe,[1] Forsyth[2] and Ley.[3] In this letter we describe model studies related to a strategy for the synthesis of the C-19 to C-30 segment. This segment encompasses the most densely functionalised region (C-22 to C-27) which contains five asymmetric centres. Disconnection of okadaic acid **1** between C-18 and C-19 yields nucleophilic **2** and electrophilic **3** fragments which would be viable synthons if suitably protected and/or activated. A synthetic equivalent of the majority of fragment **3** can in principle be constructed by using the two major modes of reactivity of allylstannanes. The C-27 centre is formed by free radical[4] allylation using **6** on the *exo*-face of the 1,6-anhydrosugar **5** and the C-22 centre by electrophilic cleavage using **4** of the 1,6-anhydro ring with inversion of configuration. The order of these steps is obligatory because the stereoselectivity of allylation at C-27 is dependant on the presence of the 1,6-anhydro linkage.[5] The Isobe[1] and Forsyth[2] syntheses, create the C27–28 bond by addition of an anion to a C-27 aldehyde.



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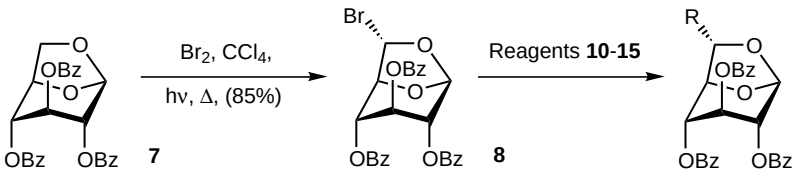
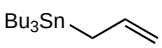
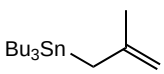
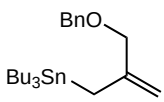
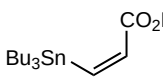
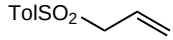
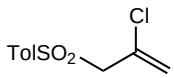
In both cases the C-27 hydroxyl group was formed with predominantly the wrong stereochemistry, which was remedied by oxidation to the ketone and reduction. In the Ley synthesis,[3] construction of the C26–27 bond yields a comparable ketone which is reduced as in the other two syntheses. Thus the proposed free radical alkylation *potentially* represents a distinct improvement, over previous syntheses. The electrophilic allylation parallels comparable steps in the Isobe and Forsyth syntheses, which construct the same bond using allyltrimethylsilane in a Ferrier rearrangement or by displacement of an anomeric methoxy group, respectively.

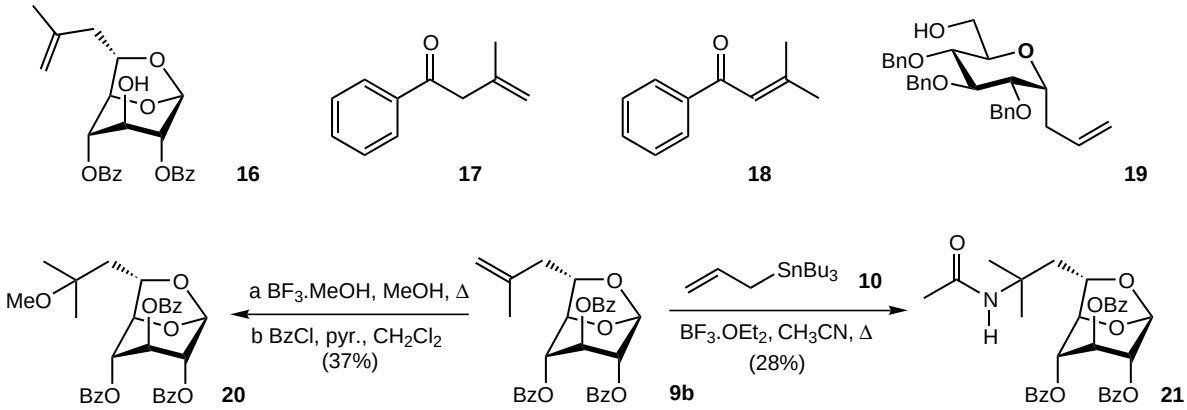
Model studies commenced with the photobromination of readily available tri-*O*-benzoyl-1,6-anhydro-β-D-glucopyranoside (tri-*O*-benzoyl-levoglucosan) **7**.[6] The stereochemistry required for okadaic acid synthon **5** is β-D-altro- or -ido-; however, tri-*O*-benzoyl-mannosan[7] and -galactosan[8] also undergo photobromination exclusively at the 6-*exo*-position, which provides some reassurance that other stereoisomers will react similarly. Free radical alkylation of **8** with allyltri-*n*-butylstannane **10** gave the desired *exo*-adduct **9a**[9] in fair yield. The stereochemistry at C-6 was inferred from the chemical shift and coupling pattern of 6-H. The 6-*endo*-proton in tri-*O*-benzoyl-levoglucosan **7** (δ 4.4) is downfield relative to the 6-*exo*-proton (δ 4.0, $^3J_{5,6}=6$ Hz) and has no appreciable coupling to 5-H. Similarly the 6-protons in the adducts **9a**–**f** have chemical shifts in the range δ 4.5–4.8 and no measurable coupling to 5-H.

Table 1. Free radical alkylation of tri-*O*-benzoyl-6-*exo*-bromo-levoglucosan **8**



Entry	Reagent	Reagent prep. ref.	Method	Product	Yield (%)	Mp (°C)
1	 **10**	10	A	**9a**	47	120–121
2	 **11**	10	A, B	**9b**	48	121–123
3	 **12**	11	A, B	**9c**	46	89–93
4	 **13** R' = Me or Et	12	A	**9d** **9e**	35, 24 31, 23 *trans*,*cis*	85–87, oil 77–79, oil
5	 **14**	13	C	**9a** **7**	67 3	As above 197
6	 **15**	13	C	**9f** **7**	71 4	119–121 As above

Reagents and conditions: Method A: **8** (1 equiv.), stannane **10**–**13** (2.5 equiv.), AIBN (0.16 equiv. every 8 h), PhMe, 96–100°C, 36 h, hexane/CH_3CN partition,[14] method B if applicable, column chromatography, crystallisation; Method B: BzCl (4 equiv.), pyr. (15 equiv.), CH_2Cl_2; Method C **8** (1 equiv.), sulphone **14** and **15** (3 equiv.), PhMe, 96–100°C, Bu_3SnH by syringe pump over 20 h, 7 h, column chromatography, crystallisation. All yields refer to analytically pure materials.



To our surprise, free radical alkylation with the 2-methylallylstannane **11** gave a complex mixture of the anticipated adduct **9b** and debenzoylated adducts and this also occurred with the benzyloxymethylallylstannane **12**, but to a much lesser extent. In one run, a small amount of a crystalline product **16** (mp 144–147°C) was isolated and the structure determined by X-ray crystallography. Although this material was part of a mixture of ill defined composition, it is the product expected on the basis of a nucleophilic cleavage mechanism.[15] Rebenzoylation of the mixture (Table 1, method B) before final purification afforded adequate yields of the desired adducts **9b** and **9c**. We have been unable to find any precedents for the cleavage, but plausibly, the high nucleophilicity of the stannanes **11** and **12**, catalysis by tri-*n*-butyltin bromide and high temperatures suffice to promote this otherwise unfavourable reaction. Both the stannane and tri-*n*-butyltin bromide seem to be essential for the cleavage. Refluxing tri-*O*-benzoyl-levoglucosan **7** with 2-methylallylstannane **11** for 48 h at 96°C occurred without change. However, methyl benzoate under the same conditions for 37 h gave an intractable mixture, but was unchanged when refluxed (80°C, C_6D_6) with tri-*n*-butyltin bromide for 5 days. We were not able to identify conclusively the anticipated by-product **17** or the conjugated analogue **18** in any of the reactions.

The *cis*-β-stannyl acrylates **13a** and **13b** yielded 70:30, *trans*,*cis* crude mixtures of the adducts **9d** and **9e**. When the reaction was run in toluene-d_8, and monitored directly by ^{1}H NMR, *cis*:*trans* isomerisation of the reagents **13a** and **13b** occurred more rapidly than alkylation and the equilibrium value was circa 70:30, *trans*:*cis*. Isomerisation can presumably be attributed to reversible addition of the tri-*n*-butyltin radical. The sulfones **14** and **15** gave reaction mixtures which were easier to purify, albeit with some concomitant reduction of tri-*O*-benzoyl-6-*exo*-bromo-levoglucosan **8**, but there was no detectable reduction of the vinyl chloride substituent.

Cleavage of the 1,6-anhydro-linkage of a tri-*O*-benzoyl-levoglucosan derivative was anticipated to be challenging. The 2-*O*-substituent lies *anti* to the bond undergoing cleavage and, with a fully formed oxonium ion, participation of the 2-benzoate group would likely lead to substitution with overall retention of configuration at C-1, rather than the desired inversion (cf. **3**).[16] Moreover the discovery of ester cleavage during free radical alkylation did not augur well for the proposed reaction. Tri-*O*-benzoyl-levoglucosan **7** was unchanged upon treatment with the boron trifluoride methanol adduct in methanol or with boron trifluoride etherate in acetonitrile and allyltri-*n*-butylstannane **10** at 0°C to room temperature, whereas at reflux the allylmethyl derivative **9b**, gave the addition products **20** and **21**. Attempts to functionalise stereoselectively the side chain by epoxidation were unrewarding. Treatment of the alkenes **9a**–**c** with *m*CPBA in methylene chloride at −10 or −78°C gave mixtures of diastereomeric epoxides in the range 50:50 to 42:58 (75–78% yield).

Benzylated 1,6-anhydrosugars have been cleaved with allyltrimethylsilane[17,18] and acyloxy-[19] or methoxy-[20] allylsilanes. We envisaged that the greater nucleophilicity of allylstannanes would promote the reaction, however, despite the use of a wide range of conditions we were not able to achieve cleavage in satisfactory yields. However, tri-*O*-benzyl-levoglucosan was cleaved by allyltrimethylsilane and boron trifluoride etherate in acetonitrile to give the α-*C*-glycoside **19** as reported previously by Kishi (17%).[17]

Conclusions: Free radical alkylation of 6-bromolevoglucosan tribenzoate is highly stereoselective and delivers a product with six contiguous chiral centres. Benzoyl ester cleavage by the more nucleophilic allylstannanes **11** and **12** is an undesirable side reaction. Plausibly, electrophilic cleavage of the 1,6-anhydro linkage of substituted levo-altrosans or -idosans by allylstannanes may be more facile than with -glucosans and future work will be directed towards these compounds.

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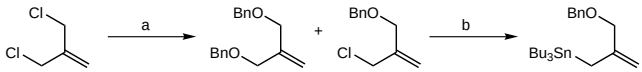
The benzyl ether stannane **12** was prepared from commercially available 3-chloro-2-chloromethyl-1-propene **22**. Investigation of a range of conditions with sodium or potassium hydride and potassium *t*-butoxide in ether or THF gave ratios of the di- and monobenzyl ethers **23** and **24** in the range 34:66 to 12:88.[21] The best yield of the monobenzyl ether **24** (68%) was obtained with potassium *t*-butoxide and 18-crown-6 in THF on a 20 g scale.



22 **23** **24** **12**

Reagents and conditions: (a) BnOH (0.9 equiv.), KO^{t}Bu (1 equiv.), 18-crown-6, THF, 0°C to rt, 12 h, chromatography (**23** 12%, **24** 68%); (b) Mg, THF, reflux, ^{n}Bu$_3$SnCl, **24** (Barbier conditions), 12 h (**12**, 85%).

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